REMARKS

The Examiner is thanked for the due consideration given the application. The specification has been amended to insert headings.

Claims 30-60 are pending in the application. Claims 30-33, 36, 39-41, 45, 46 and 51 have been withdrawn from consideration. The claims have been amended to improve the language in what is believed to be a non-narrowing fashion.

No new matter is believed to be added to the application by this amendment.

Claim Objections

The claims have been objected to as containing informalities, i.e., no periods at the end. The claims have been amended to be free from informalities.

Rejection Under 35 USC §112, Second Paragraph

Claims 34, 35, 37, 38, 42-44, 47-50 and 52-60 have been rejected under 35 USC §112, second paragraph, as being indefinite. This rejection is respectfully traversed.

The Official Action asserts that the claims recite a broad range limitation together with a narrow range limitation. However, the claims have been amended to not recite a broad range limitation together with a narrow range limitation.

Also, the claims have been amended to clarify the recitations of aromatic groups and biorecognition elements. Claim 37 has been amended to set forth a structure.

Additionally, the metes and bounds of the instant claims would be clear to one of skill in the art.

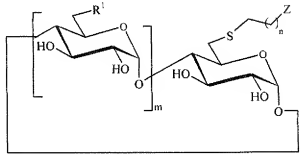
The claims are thus clear, definite and have full antecedent basis.

This rejection is believed to be overcome, and withdrawal thereof is respectfully requested.

Rejection Under 35 USC §103(a)

Claims 34, 35, 37, 38, 42-44, 47-50 and 52-60 have been rejected under 35 USC §103(a) as being unpatentable over MELLET et al. (*Chem. Eur. J.* 2002, 8, No. 9, pages 1982-1990) in view of YASUDA et al. (*Chemistry Letters* 2000, pages 706-707). This rejection is respectfully traversed.

The present invention pertains to a compound of the formula (I):



In formula (I), Z can be an NHX group, a quaternary ammonium group of the $^{+}NX_3$ form, or 

such that R can be a chemical substituent or a biorecognition element.

The present invention thus relates to cyclodextrin compounds that are designed to show simultaneously different properties:

1) biorecognition towards a specific target,

2) complexation of a host compound,

3) good solubility in water, and

4) high purity due to the high yield of an easily industrially applicable reaction.

Simultaneously obtaining these properties, i.e., multivariables, is a balance that is difficult to achieve, as the improvement of one might imply alteration of another one. This has been achieved in the invention, in particular, by means of the appropriate nature and length of the linker between the cyclodextrin and the biorecognition elements.

The Official Action asserts that MELLET et al. teach multivalent cyclodextrins with thiourea-bridged adducts that are advantageously water soluble, that the cyclodextrin association constant depends on the length and the nature of the linker, and that cyclodextrins carrying a glycodendron are useful in drug targeting.

The Official Action asserts that YASUDA et al. teach a flexible spacer arm which induces a fit of the cyclodextrin derivatives around the guest molecule, and that this linker is cited by MELLET et al. as an advantageous choice. The linker taught by YASUDA et al. is formed from thioether and amide groups, but no thiourea group.

The references of MELLET et al. and YASUDA et al. are analyzed below.

I. MELLET et al.

1) Target biorecognition

a) Linker length

MELLET et al. teach the use of thiourea linkers, which should be long enough to show a good biorecognition. No linker using both thiourea and thioether is taught by MELLET et al. The best compound obtained by MELLET et al. is compound 30 (page 1988) with an IC_{50} of 70 µM for ConA. The IC_{50} value is directly correlated to the biorecognition; low IC_{50} indicates high biorecognition.

b) Biorecognition elements multiplicity

MELLET et al. teach that the multiplication of biorecognition elements would increase the biorecognition (binding affinity). The improvement in the binding affinity is 16 fold when the number of biorecognition element is increased by 6 fold (page 1989).

Thus, the man skilled in the art is motivated to use long thiourea linkers, and is motivated to expect a 2.5 fold increase of binding affinity per additional biorecognition element.

2) Host complexation

MELLET et al. state (page 1987): "*Complexes involving guest molecules entering the cavity through the narrower rim may experience some decrease in the association constant as compared*

to the corresponding native β-CD due to the steric hindrance imposed by the substituent."

The "interesting" effect on complexation observed by YASUDA et al. is rather contradictory with this statement.

One of ordinary skill in the art would thus not combine MELLET et al. with YASUDA et al. because the two references teach away from their combination.

It is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983).

3) Water solubility

MELLET et al. clearly taught the advantage of the thiourea over the prior art in order to increase the solubility of cyclodextrin in water (page 1985).

MELLET et al. stated (page 1985): "*The scope of the thiourea-bridging strategy, actually one of the most conventional methodologies in neoglycoconjugate preparation...*". Thus, thiourea functions are well known by the man skilled in the art for their advantages in solubilising cyclodextrins in water over prior art functions (including the long known thioglycoside or thioether).

The man skilled in the art is strongly motivated to use thiourea, but not thioether, to increase the solubility of cyclodextrin.

4) Purity, Industrial application

Thioether compounds are difficult to purify and the thiourea strategy was introduced in order to improve the coupling reaction between various substituents to the cyclodextrin core and then increase the yield and purity of the prepared grafted cyclodextrin derivatives.

The most efficient compound for biological recognition prepared by MELLET et al. is compound 30 (page 1988). The synthesis of this compound was performed in 9 steps with a global yield of 8%. This yield is an improvement over the yield previously obtained in thioether compounds synthesis, but it remains too low to be interesting for industrial applications.

MELLET et al. thus teaches that the synthesis of thiourea functionalities is more efficient than the synthesis of thioether functionalities.

In conclusion, MELLET et al. teach that cyclodextrin compounds should have long linkers between the cyclodextrin core and the biorecognition elements; that binding affinity can be increased by a 2.5 fold per additional biorecognition elements, and that the narrow rim of a cyclodextrin should not be sterically hindered in order to afford good host molecule complexation. MELLET et al. also teach the superiority of the thiourea function, over the thioether function, for water solubility and synthesis efficiency of the cyclodextrin derivative.

Thus the man skilled in the art is motivated by MELLET et al. to use thiourea over thioether.

II. YASUDA et al.

1) Target biorecognition

Figure 4 in YASUDA et al. (page 707, left column) shows how the linker fits around the host molecule. It also suggests how all the galactosyl moieties, which act as biorecognition elements, are packed together. Such packing, by fixing the recognition element and thereby limiting their flexibility and mobility, is expected to have unfavorable effects on the binding properties (MELLET et al. page 1987, right column) by reducing the possibility of interaction with the active site of a biological receptor. This is an effect which is equivalent to decreasing the linker length.

Thus, one could consider that the linker taught by YASUDA et al. reduces the affinity of the cyclodextrin biorecognition element for a receptor. Thus, it would not be recognized as an improvement of the art (MELLET et al.) by the skilled artisan since an efficient biorecognition towards a given target is not fulfilled.

2) Host complexation

According to the Official Action: "*The linkage employed by Yasuda et al. was mentioned as an advantageous choice by Mellet et al.*".

However, this statement represents a misunderstanding of the technology of MELLET et al.

MELLET et al. failed to refer to linkers described in the document by YASUDA et al. as "*advantageous*". MELLET et al. stated: "*Thus, for guest molecules entering the cavity through the primary hydroxyl groups face, the association constant will be expected to drastically decrease. Interestingly, the opposite effect has been observed for the complexation of the anticancer drug doxorubicin with a heptalactosyl β-CD conjugate of type* ***16*** *having flexible spacer arms, which has been ascribed to the induced fit of the heptavalent glycocluster around the guest molecule.*"

MELLET et al. observed that the linker taught by YASUDA et al. is ***interestingly*** increasing the complexation of the host molecule within the cyclodextrin, in contrast to what could be assumed.

Thus, the man skilled in the art would be motivated rather to use the YASUDA et al. linker over the MELLET et al. linker, in order to increase the host compound stabilization with the cyclodextrin.

3) Water solubility

YASUDA et al. fail to give any information about the solubility of the compound they described. It should be noted that the man skilled in the art knows that thiourea

functionalities increase the solubility of cyclodextrin in water more than sugar and amide moieties do.

As YASUDA et al. use glucono-amide moieties instead of thiourea, the man skilled in the art would assume that the linker of YASUDA et al. is less soluble than the linker described by MELLET et al.

4) Purity, Industrial application

No experimental description of the YASUDA et al. linker is given in the Chem. Lett. paper. The only characterization is a peak in FABMS, and no synthesis yield is provided.

Purification was laboriously performed by preparative HPLC, which is applicable only for small quantities but not for a large scale synthesis (industrial). Furthermore, such a way of purification suggests a large number of impurities, which makes purification by classical chromatography (*e.g.* silica gel) inefficient. It should be noted that no indication of purity is given, as a mass spectrum does not preclude the presence of contaminants such as isomeric compounds or compounds showing defaults or irregularities in the structure.

Thus the man skilled in the art would conclude that the linker prepared by YASUDA et al. is difficult to purify and could not be obtained in large quantities.

In conclusion, YASUDA et al. teach a linker (glucono-amide thioether) which, by comparison to the linker taught by MELLET et al., shows a better complexation of the host molecule, but shows

a lower biorecognition of the biological target, a lower water solubility and involves a difficult synthesis. Thus, the advantage of YASUDA et al.'s linker is outweighted by its disadvantages, and the man skilled in the art would not be motivated to use YASUDA et al.'s linker.

III. Chronology in linker synthesis

1) Thioether

Thioglycosides (and then thioethers) were first used in 1989 in order to improve the solubility of cyclodextrins in water. The thioether functionality was found convenient to introduce a carbohydrate moiety onto the cycodextrin core, which was expected to increase the solubility in water due to hydrogen bonding.

Two difficulties appeared from this approach; thioglycosides were difficult to purify and the biorecognition with the receptor was low.

2) Longer linker

Longer linkers were introduced in order to increase the biorecognition. The strategy was successful but the synthesis and purification remained difficult.

3) Thiourea

A more reactive function was thought to increase the reaction yield and reduce by-products, thus simplifying the purification. The new strategy was to replace the thioether linkage by a thiourea linkage. Thiourea functions appeared to be easier to obtain and the reaction yield was successfully

increased while the purification stage was made easier. An interesting feature of the thiourea was their ability to increase the solubility of cyclodextrins in water.

These two advantages (synthesis and solubility) set the superiority of the thiourea strategy over the thioether strategy, and the thiourea bridging strategy became the most conventional methodology in neoglycoconjugate preparation (MELLET et al. at page 1985).

In conclusion, the man skilled in the art is not motivated to use thioether anymore since the advantage of the thiourea function over the thioether function are well known in the prior art.

IV. Technical gap between the invention and the prior art

1) Outdated technique

Thioether linkers are known to be less efficient than thiourea ones with respect to the solubility and ease of synthesis of cyclodextrin derivatives. Thus, the man skilled in the art is not motivated to use an outdated technique.

2) Biorecognition

It is to be noted that compound 2 of the present invention differs from the best compound in the prior art (compound 30, MELLET et al., page 1988) only by the nature of the linker. Compound 2 linkers involve both thioether and thiourea functionalities whereas compound 30 linkers involve two thiourea functionalities only.

Thus assuming that the man skilled in the art, against all the teaching of the prior art, would try to prepare a cyclodextrin compound with a linker comprising both thiourea and thioether, the obtained cyclodextrin would be compound 2 described in the present invention.

The IC_{50} value of compound 30 is 70 µM, whereas IC_{50} value of compound 2 is 175 µM. Thus, one skilled in the art would conclude that these results go in the same way as the prior art teaching (superiority of a pure thiourea linker), and there would be no motivation to further investigate thioether-thiourea mixed linkers.

3) Biorecognition elements

MELLET et al. teach a 2.5 fold increase of binding affinity per additional biorecognition elements (MELLET et al., page 1989).

Compound 2 of the present invention has an IC_{50} value of 175 µM and 6 biorecognition elements. Compound 4 of the present invention has 3 fold more biorecognition elements than compound 2, yet compound 4 IC_{50} value is 5 µM. The IC_{50} has been increased by 11.5 fold per additional biorecognition elements.

This unexpected biorecognition improvement was not taught nor suggested by MELLET et al. The present invention thus shows unexpected results over MELLET et al. that would rebut any unpatentability that could be alleged.

In conclusion, one skilled in the art was not motivated to use an outdated technique (thioether) that was known to be less effective than a recent one (thiourea).

The prior art neither teaches nor motivates one skilled in the art to combine thioether and thiourea in a new linker.

The prior art neither teaches nor infers that combining this new linker with more biorecognition elements would give cyclodextrin compounds with an unexpected increase in biorecognition.

The prior art furthermore fails to teach or suggest that combining thioether and thiourea functionalities would result in such drastic synthetic advantages over thiourea linkers for cyclodextrins decoration as taught in the present application.

Thus, the present invention should be considered patentable over the teaching of the prior art.

One of ordinary skill would thus fail to produce a claimed embodiment of the present invention from a knowledge of MELLET et al. and YASUDA et al., and a *prima facie* case of unpatentability has thus not been made. Even if unpatentability could be alledged, this unpatentability would be rebutted by the unexpected results of the present invention, as discussed above.

This rejection is believed to be overcome, and withdrawal thereof is respectfully requested.

Conclusion

The Examiner is thanked for considering the Information Disclosure Statement filed March 30, 2006 and for making an initialled PTO-1449 Form of record in the application.

Prior art of record but not utilized is believed to be non-pertinent to the instant claims.

It is believed that the rejections have been overcome, obviated or rendered moot and that no issues remain. The Examiner is accordingly respectfully requested to place the application in condition for allowance and to issue a Notice of Allowability.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

YOUNG & THOMPSON

Robert E. Goozner, Reg. No. 42,593
Customer No. 00466
209 Madison Street, Suite 500
Alexandria, VA 22314
Telephone (703) 521-2297
Telefax (703) 685-0573
(703) 979-4709

REG/lk